

Half-Life of Blood Carboxyhemoglobin after Short-Term and Long-Term Exposure to Carbon Monoxide

Takeshi Shimazu, MD, Hisashi Ikeuchi, MD, Hisashi Sugimoto, MD, Cleon W. Goodwin, MD, Arthur D. Mason, Jr., MD, and Basil A. Pruitt, Jr., MD

Background: In models of smoke inhalation injury and carbon monoxide poisoning blood carboxy-hemoglobin (COHb) levels decrease faster than predicted by the generally recognized half-life of COHb. We studied the effects of duration of exposure to carbon monoxide (CO) on the subsequent CO elimination.

Methods: Each of four sheep were insufflated with CO gas mixtures either for a few minutes (short-term exposure) or for several hours (long-term exposure),

then ventilated with air for 3 hours. Serial COHb concentrations were analyzed by using a two-compartment, single central outlet mathematical model.

Results: Short-term exposures exhibited biphasic decreases of COHb concentration compatible with a two-compartment model; an initial rapid decrease (half-life 5.7 ± 1.4 minutes) was followed by a slower phase (103 ± 20.5 minutes). Long-term exposures exhibited almost monophasic decreases, which were never-

theless compatible with the model (half-life, 21.5 ± 2.1 and 118 ± 11.2 minutes).

Conclusion: This study demonstrated different patterns of CO elimination curve, which suggests distribution of CO to two compartments having different rates of equilibration.

Key Words: Carbon monoxide, Carboxy-hemoglobin (COHb), Smoke inhalation injury, Half-life, Two compartment analysis.

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Carbon monoxide (CO) is one of the most toxic components of smoke and is responsible for the substantial part of the approximately 10,000 persons who die annually of fire-related injuries.^{1,2} Although CO poisoning is the most frequent immediate cause of death from fire, there are still controversies on the mechanism of CO toxicity, i.e., CO toxicity in relation to the route of absorption, individual susceptibility to CO, and influence of CO on the cytochrome systems.^{3–5} The apparently short half-life of blood carboxy-hemoglobin (COHb) in patients or experimental animals exposed to carbon monoxide for a relatively short period of time is another question to be answered.^{6,7}

In CO poisoning, blood COHb concentrations are described in reviews and textbooks, to exhibit a single exponential (i.e., linear on a semilogarithmic scale) decrease during the elimination process.^{8–10} However, a few reports have described a biphasic decrease in COHb concentrations with a shorter half-life during the early phase of elimination after a short exposure to CO.^{11,12} We have shown in a preliminary report that blood COHb shows a biphasic decrease after short-term (3–8 minutes) exposure, which was compatible with a two-compartment model and that the biphasic nature of the elimination curve was not altered by various factors that might affect the half-life of blood COHb such as peak COHb level, mode of exposure to CO, or concentration of oxygen used during the CO elimination phase.¹³

In this study, we compared the blood COHb elimination curves after short-term and long-term exposure to CO, and analyzed the dynamics of the CO elimination process using a two-compartment, single central outlet mathematical model. The clinical implications of the difference in the CO elimination curve, the theoretical background of the elimination of CO from the blood, and the anatomic and physiologic characteristics of the two compartments are discussed.

MATERIALS AND METHODS

Animals and Preparations

Eight female sheep weighing 39.9 ± 3.8 kg (range, 35 to 45 kg) were used in this study. The animals were anesthetized and catheterized by using sterile technique for arterial and central venous lines 1 to 3 days before experiments. They recovered from anesthesia, and were extubated and allowed to breathe spontaneously until the time of the experiment.¹⁴

On the day of the experiment, the sheep were intubated and anesthetized. Anesthesia was induced with methohexital

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From the Department of Traumatology (T.S., H.I., H.S.), Osaka University, Medical School, Osaka, Japan, and the US Army Institute of Surgical Research (C.W.G., A.D.M., B.A.P.), Fort Sam Houston, Texas.

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Table 1 Various Conditions of Exposure to Carbon Monoxide

Group	Sheep No.	Exposure Duration	Exposure Mode	Tidal Volume (mL/kg)	CO Concentration	Peak COHb Levels (%)
S-1	1,2	3 min	Intermittent	30	2%	30.5, 30.6
S-2	3,4	1.5 min	Continuous	15	2%	38.8, 24.8
L-1	5,6	5 h	Continuous	15	500 ppm	34.1, 34.2
L-2	7,8	10 h	Continuous	15	500 ppm	36.6, 35.3

sodium (9 mg/kg) and maintained with alpha-chloralose (0.05 g/kg, Calbiochem, La Jolla, CA). The sheep were paralyzed with pancuronium bromide. Half of the initial doses of chloralose and pancuronium were added as needed. The animals were then positioned prone and artificially ventilated by using a volume-limited ventilator (Harvard dog ventilator model 613, Harvard Apparatus Company, South Natick, MA) with a tidal volume of 15 mL/kg and respiratory rate of 12 per minutes. After 2 hours of stabilization, the animals were exposed to CO. All of the experimental procedure of exposure to CO and study of the elimination process were performed under general anesthesia.

This study was approved by the Institutional Review Board for protocol and animal use. In conducting the research described in this report, the investigators adhered to the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals in the "Guideline for the Care and Use of Laboratory Animals" (Department of Health, Education, and Welfare Publication no. (NIH)85-23, revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20892).

Exposure to Carbon Monoxide

The sheep were divided into two groups of four each: a short-term exposure (S) group and a long-term exposure (L) group (Table 1). The S group was insufflated with a high CO gas mixture that consisted of 12.6% oxygen, 5.2% carbon dioxide, 80.2% nitrogen, and 2.0% carbon monoxide. The L animals were ventilated with a low CO gas mixture that contained 500 ppm (0.05%) CO in the air (20.9% oxygen and nitrogen balance).

Two of the S animals were ventilated with the high CO gas mixture for 3 minutes with intermittent room air ventilation by using a tidal volume of 30 mL/kg and respiratory rate of 13 per minute as described in detail previously (S-1 subgroup).¹⁴ The other two were insufflated with the high CO gas mixture continuously for 1.5 minutes (S-2 subgroup) with a tidal volume of 15 mL/kg and respiratory rate of 12 per minutes. The L animals were ventilated continuously with the low CO gas mixture for either 5 hours ($n = 2$, L-1 subgroup) or 10 hours ($n = 2$, L-2 subgroup) with a tidal volume of 15 mL/kg and respiratory rate of 12 per minute.

The CO exposures were made using the volume-limited ventilator for subgroups S-2, L-1, and L-2, and a volume-adjustable metal syringe for the subgroup S-1 by changing the

circuit of inspiratory gas intake from ambient air to pooled CO gas mixtures.¹⁴

Carbon Monoxide Elimination

After exposure to CO, the sheep were ventilated with room air free of CO for 3 hours. A tidal volume of 15 mL/kg and a respiratory rate of 12 per minute were used during this CO excretion process. Arterial and mixed-venous blood were drawn before exposure to CO, at the end of exposure (time 0), 7.5 minutes after exposure, 15, 30, 45, 60, 90, 120, 150, and 180 minutes after exposure. Blood gas analysis and blood COHb measurement were performed by using an IL 1303 pH/blood gas analyzer and an IL 282 CO-Oximeter (Instrumentation Laboratories, Inc., Lexington, MA). The animals were killed at the end of the experiments and necropsies were performed for the evaluation of the cardiopulmonary system.

Two-Compartment Analysis

CO elimination process was analyzed by using a two-compartment (central and peripheral), single central outlet mathematical model (Fig. 1). The sum of two exponentials ($Y = A \times \exp(-BX) + C \times \exp(-DX)$) was fitted to the serial blood COHb concentrations by using nonlinear regression with a least squares method.¹⁵ Refer to Figure 1 for mathematical background of two-compartment analysis.^{16,17}

RESULTS

Exposure to CO under various conditions resulted in comparable levels of peak blood COHb (24.8–38.8%) (Table 1). Blood pressure, heart rate, and cardiac output showed mild to moderate increase, but all the animals remained hemodynamically stable. There were no significant changes in the blood hemoglobin and serum bicarbonate concentrations in any animal during the experiment.

CO elimination curves after short-term exposure (Fig. 2) and long-term exposure (Fig. 3) were apparently different. In the former, biphasic decrease with rapid initial decrease followed by a slower phase was observed in the both S-1 and S-2 subgroups. The mode of exposure did not affect the nature of the elimination curve after short-term exposure.¹³ The shape of the elimination curves suggests that the distribution and elimination of CO from the blood are best explained by a two-compartment mathematical model (Fig. 1). On the other hand, after long-term exposure, CO elimination seemed to be virtually monoexponential with a single rate

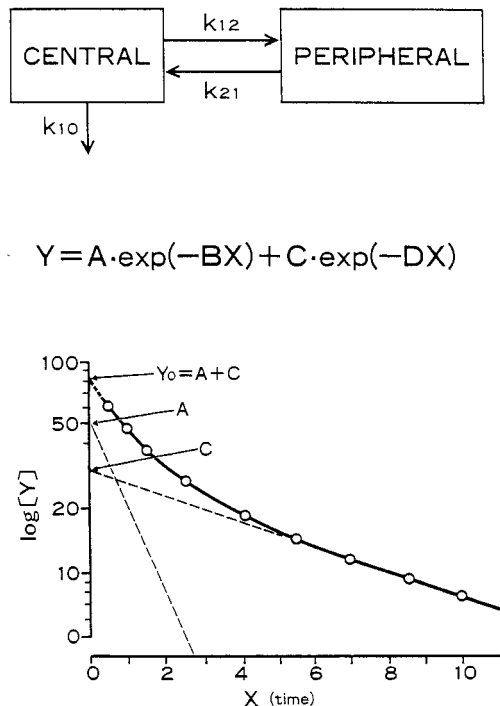


Fig. 1. The two-compartment, single central outlet mathematical model. Concentration (Y) in the central compartment at given time (X) is expressed by an equation consisting of two exponentials: $Y = A \times \exp(-BX) + C \times \exp(-DX)$, where X and Y are time in minutes, and COHb concentrations are in percentages. A , B , C , and D are constants and are obtained by fitting the elimination curve. Rate constants k_{12} and k_{21} are the apparent first-order intercompartmental distribution rate constants, and k_{10} is the apparent first-order elimination rate constant from the central compartment. Rate constants are expressed using A , B , C , and D ; $k_{21} = (AD + BC) / (A + C)$; $k_{10} = BD / k_{21}$; $k_{12} = B + D - k_{21} - k_{10}$. Half-life in the distribution ($T_{1/2}(d)$) and elimination ($T_{1/2}(e)$) phases are obtained by the following equation:¹⁶ $T_{1/2}(d) = 0.693 / B$; $T_{1/2}(e) = 0.693 / D$.

constant. However, a close scrutiny revealed higher rate early in the postexposure period, which suggests distribution to two compartments having different rates of equilibration.

Two-compartment analysis revealed that the CO elimination curves (observed values) were compatible with a two-compartment model (predicted values) in both of the groups. Table 2 summarizes the constants A to D of the fitted elimination curves (Fig. 1) and the time constants for the first (distribution) and the second (elimination) phases. Constants A and C are zero-time intercepts and may be used to estimate the volume (dilution space) under certain conditions, for example after rapid intravenous injection of a drug.¹⁸ Similarly, B and D are time constants that give the half-life of each phase. The half-life of the initial and the second phase in the S group were 5.7 ± 1.4 minutes and 103 ± 20.5 minutes, respectively. Those in the L group were 21.5 ± 2.1 minutes and 118 ± 11.2 minutes, respectively.

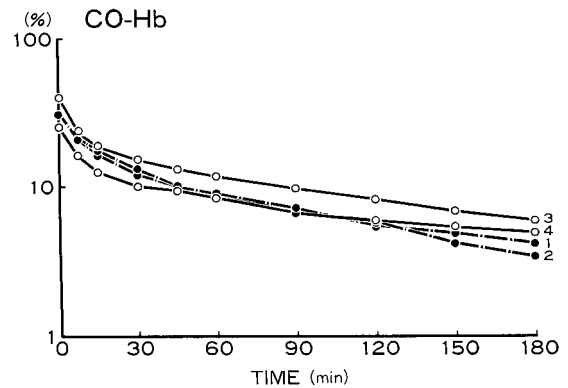


Fig. 2. Changes in blood COHb after short-term exposure to CO. Serial changes of blood COHb (percentages) of the S group are plotted on a semilogarithmic scale against time (minutes) during the 3-hour excretion period. Closed circles represent subgroup S-1, and open circles S-2. Numbers on the right of each curve correspond to the sheep number in Table 1. A biphasic decrease was observed in the both subgroups with a rapid initial decrease followed by a slower phase. Such elimination curves suggest distribution to two compartments. Note that the CO elimination curves after short-term exposure are different from the generally accepted shape that is linear on a semilogarithmic scale.

Pathologic examination revealed scattered myocardial necrosis in all animals exposed to CO for 5 or 10 hours, whereas none of the S animals had such changes. The respiratory system was histologically intact in all animals.

DISCUSSION

The dynamics of the CO elimination process after short-term and long-term exposure to CO has been analyzed by using a two-compartment model. There seems to be a misconception about the half-life of blood COHb after short-term exposure to CO. It is generally believed that blood COHb

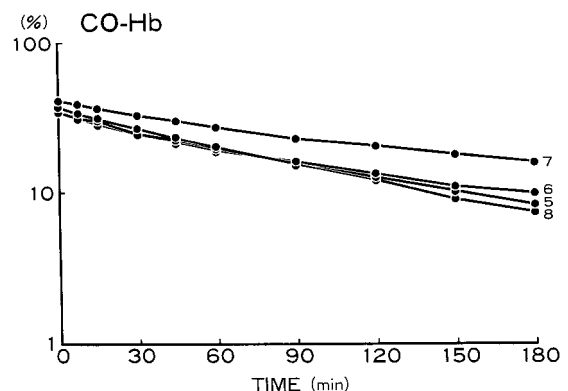


Fig. 3. Changes in blood COHb after long-term exposure to CO. Blood COHb in the L group is shown on a semilogarithmic scale as in Figure 2. In this group, the CO elimination curve is almost linear. However, a slightly higher rate of decrease is recognized during the early phase, which suggests that CO distributes also in the L group to two compartments having different rates of equilibration.

Table 2 Constants of the Fitted Elimination Curve Defined in Figure 1^a

Group	No. of Sheep	A	B	C	D	T1/2(d)	T1/2(e)
S	4	16.7 ± 3.3	0.13 ± 0.0033	14.4 ± 2.6	0.0069 ± 0.0014	5.65 ± 1.35	102.8 ± 20.5
L	4	7.8 ± 2.8	0.043 ± 0.022	27.2 ± 2.9	0.0065 ± 0.0012	21.5 ± 2.06	117.8 ± 11.2

^a A to D represent constants used to describe the elimination curve as a sum of two exponentials as $Y = A \times \exp(-BX) + C \times \exp(-DX)$. Refer to Figure 1 and text for detail.

concentrations decrease in a single exponential manner after CO poisoning of any duration.^{8,18} However, such elimination curves were originally obtained in experiments in which subjects were exposed to CO for several hours.¹⁹ In those cases, the blood COHb levels seem to follow a single exponential curve very closely as shown in Figure 3. The same elimination curve has been applied to patients with smoke inhalation injury who were exposed to CO for a relatively short period of time. It is only recently that a significantly shorter half-life of blood COHb during the early phase of CO excretion has been identified in smoke inhalation injury.^{6,7} Moreover, some of the early studies on changes of blood COHb levels after acute CO poisoning have already described a biphasic decrease of the blood COHb.²⁰

In the clinical setting, such an initial rapid decrease of blood COHb would be facilitated by hyperventilation of the patients caused by posttraumatic agitation and hypoxia if any. The toxicity of CO and its treatment might need reevaluation, at least in patients who have been exposed to gas containing relatively high concentration of CO for short period of time. In those cases, blood COHb readily exceeds 50%, which is supposed to lead to collapse, according to the well-known table of symptoms associated with varying levels of CO poisoning.⁸ However, in our animal studies acute CO poisoning reaching 50 to 60% of COHb did not produce detrimental effects, and the half-life of blood COHb during the early phase was less than 10 minutes even when ventilated with air.^{7,14} It is of interest that changes of blood COHb concentration after 5 or 10 hours of exposure still showed a slightly shorter half-life in the postexposure period, which makes the elimination curve not exactly the same as the generally assumed single exponential decrease (Fig. 3). This finding does not mean that patients with admission blood COHb levels of 50% should receive less care, but rather we should consider that their peak COHb levels on the scene could have been much higher than we would usually estimate. Clark et al. devised a nomogram for fire victims to estimate the peak COHb levels at the scene from the measured COHb levels and time interval between exposure and measurement.²¹ However, this nomogram might still underestimate the original peak COHb levels because they constructed it by assuming monoexponential decay of COHb with the half-life of 4 hours for room-air breathing subjects or 3 hours for subjects administered oxygen, which means initial rapid decrease of COHb is not taken into account. Thus, duration of exposure to CO as well as peak COHb levels should be considered in

estimating the severity of CO poisoning and indications for various treatments.

Various studies have been published on the prediction of the COHb levels resulting from CO exposure by using a theoretical uptake-elimination equation. The fundamental equation was established by Coburn et al. in 1965. They made certain assumptions and solved the equation (CFK equation), which made it possible to predict the steady state value of COHb.²² However, the CFK solution cannot be applied to the prediction of the COHb levels during CO uptake and elimination, because the equation is based on the assumption that the oxyhemoglobin (O₂Hb) concentration is constant with time and independent of the COHb concentration. Thus, the application of the CFK solution to predict the COHb levels were confined to low levels of COHb. Tyuma et al. solved the CFK equation analytically with less restrictive assumptions.²³ The new assumptions they made were there is no significant amount of deoxyhemoglobin, i.e., hemoglobin is always saturated with O₂, CO, or both, and the following relation is obtained. $\text{COHb} / \text{O}_2\text{Hb} = Y / (1 - Y)$; the rate of production of CO in the body is zero (actual production is 0.007 mL/min in normal man); and Y₀ is assumed to be zero, a mathematical condition that is essentially satisfied when P_{ACO} (partial pressure of CO in the alveolar air) is greater than 50 ppm after exposure to CO.²³ Then the equation used for the elimination process is obtained as follows: $t = C \times V_b \times M \times D \times \{(Y - Y_0) - \ln(Y / Y_0)\} / P_{\text{CO}_2}$; where t, time; C, binding capacity of blood (mL/mL) to oxygen or CO = concentration of hemoglobin (g/mL) × 1.39 (mL/g); V_b, total blood volume (mL); M, partition constant between CO and oxygen for hemoglobin (Haldane constant, approximately 250 for man) $D = 1 / D_L + 713 / V_A$ at 37°C; D_L, pulmonary diffusing capacity (mL/min per mm Hg); V_A, alveolar ventilation (mL/min); Y, fractional saturation of hemoglobin with CO; Y₀, value of Y at t = 0; P_{CO₂}, mean O₂ pressure in equilibrium with O₂Hb in the pulmonary capillary.

COHb at any time can be predicted according to the above equation by substituting appropriate values for C, V_b, M, D, P_{CO₂}, and Y₀.²³ Figure 4 represents the analytical solution of the Tyuma' equation when the peak COHb is 30%. It is noteworthy that the elimination curve derived from a theoretical analysis is not linear on the semilogarithmic scale. The rate of decrease is slightly higher in the early postexposure period, which is similar to the actual elimination curve in Figure 3. This finding indicates that the generally accepted single exponential decrease of blood COHb

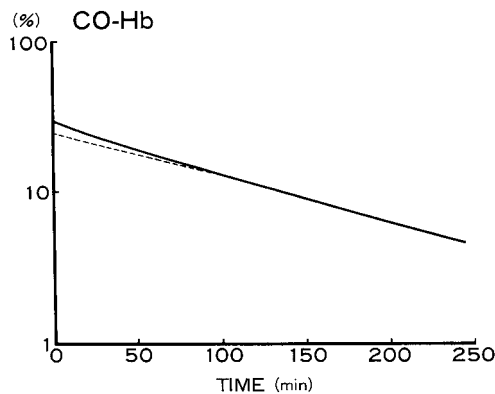


Fig. 4. COHb elimination curve obtained from a theoretical uptake-elimination equation of CO at the steady state. COHb concentration (Y) is expressed as $t = K((Y - Y_0) - (\ln(Y / Y_0)))$, where t is time and Y_0 is value of Y at $t = 0$. See text for detail.²³ Note that the theoretical elimination curve (solid line) is not linear (dotted line) on a semilogarithmic scale, closely resembling that of long-term exposure (Fig. 3).

does not exactly hold true even for cases of long-term exposure to CO.

What are the anatomic or physiologic entities of the two compartments? They could be either (1) an intravascular compartment and an extravascular compartment, or (2) well-perfused and poorly perfused intravascular compartments.^{11,12} Extravascular compartment includes myoglobin and cytochromes. The poorly perfused intravascular compartment may include the spleen and probably some part of muscle. Although in sheep the spleen may store up to 25% of the red blood cell volume in a highly concentrated form,²⁴ the spleen of the sheep was firm and small at autopsy and the blood hemoglobin level remained almost unchanged in this study.

In our previous study, we compared the amount of CO absorbed during short-term exposure by two methods.¹³ The respiratory method measured pooled inspiratory and expiratory CO contents by using a gas chromatography-mass spectrometer and a spirometer, and then took the difference as the absorbed amount of CO. The COHb method estimates the amount of CO taken into the blood by subtracting the COHb level before exposure from the peak COHb level and then multiplying by the estimated blood volume of the sheep.²⁵ The two values agreed well, and there was no consistent tendency that the values determined by the COHb method were less than those determined by the respiratory method. This means that the capacity of the central compartment could be satisfactorily explained by hemoglobin alone, suggesting that it does not involve a significant amount of extravascular components, which would be attributable to the binding capacity of myoglobin and cytochromes.

As O₂ and CO bind to heme-protein, the iron content of each of the components would provide rough estimation of the ratio of the capacity in the components. The iron content

of hemoglobin, myoglobin, and enzymes (includes cytochromes) is 3,050 mg, 430 mg, and 10 mg, respectively, for men and 1,700 mg, 300 mg, and 10 mg for women.²⁶ Thus, the capacity for CO in the extravascular components is approximately 1/6 of that of hemoglobin (the intravascular component).²⁷ The ratio of the volume (capacity) of the central and the peripheral compartments (V_c/V_p) is calculated as B/k_{10} .¹⁶ The V_c/V_p obtained from the short-term exposure and long-term exposure were 9.6 ± 4.0 and 5.3 ± 2.2 , respectively. These values, particularly that of the long-term exposures show good agreement with the ratio of 1 to 6 estimated from the iron contents. The small difference between these estimations might be attributable to such factors as the difference of species, release of red blood cells from the spleen, and alterations in blood volume caused by capillary permeability change associated with CO poisoning.^{24,28} It is also possible that the peripheral compartment consists partly of extravascular tissue and partly of intravascular poorly perfused tissue.

Myocardial necrosis observed only in animals exposed to CO for several hours emphasizes that CO toxicity is not determined by peak COHb alone. Toxicity of CO would be better represented by the area under the COHb elimination curve ($\Sigma (\text{COHb} \times \text{duration})$) rather than the peak COHb level. And cytochrome inhibition determined by CO partial pressure in specific peripheral tissue and its duration might be related to the long-term sequelae such as neurologic complications, for which we have no indices to predict at this moment.

In conclusion, the apparently different shapes of the CO elimination curves after short-term and long-term exposures are both compatible with a two-compartment model. Theoretical analysis of the CO excretion process indicated that the elimination curve is not precisely linear on a semilogarithmic scale and, therefore, is not a simple exponential function. Initial rapid decrease of COHb levels after short-term exposure would be attributable to both excretion from the lung and distribution of CO to the peripheral compartment, although the anatomic and physiologic entity of the two-compartment model requires further investigation.

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